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- Fetal blood vessel count increases in compensation of hypoxia in premature placentas
- Ethyl *p*-methoxycinnamate from *Kaempferia galanga* inhibits angiogenesis through tyrosine kinase
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- High toluene exposure risk increases risk of olfactory dysfunction in furniture workers

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Campbell NRC, Gilbert RE, Leiter LA, et al. Hypertension in people with type 2 diabetes: update on pharmacologic management. Can Fam Physician 2011;57:997-1002.

2. Corporate author

Diabetes Prevention Program Research Group. Ten year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009;374:1677-86. doi:10.1016/S0140-6736(09)61457-4.

3. Volume with supplement

Maeshiro R, Koo D, Keck CW. Patients and populations: public health in medical education. Am J Prev Med 2011; 41Suppl 3:S145-S318. DOI: http://dx.doi.org/10.1016/j.amepre.2011.07.010.

4. Electronic journal without page numbers

Santos CAST, Fiaccone RL, Oliveira NF, et al. Estimating adjusted prevalence ratio in clustered cross-sectional epidemiological data. BMC Med Res Method 2008;8:80. doi:10.1186/1471-2288-8-80.

Books and Other Monographs

1. Editor(s), compiler(s) as author

Gilstrap LC, Cunningham FG, VanDorsten JP, editors. Operative obstetrics. 4nd ed. New York: McGraw-Hill;2010.

2. Chapter in a book

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill;2010.p.93-113.

3. Conference paper

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, et al. editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer;2002.p.182-91.

4. Dissertation

Hos J. Mechanochemically synthesized nanomaterials for intermediate temperature solid oxide fuel cell membranes [dissertation]. Crawley, Western Australia: University of Western Australia;2005.

Electronic Material

1. Electronic documents

Murray G. A duty of care to children and young people in Western Australia: Report on the quality assurance and review of unsubstantiated allegations of abuse in care:2005. Available at: http://www.community.wa.gov.au/NR/rdonlyres/851183A4-A822-4592-AB66-CietsC410E453AEEC/0/DCDRPTGwennMurrayreportwithcover2006.pdf Accessed April 12, 2008.

2. Journal article on the internet

Sillick T J, Schutte NS. Emotional intelligence and self-esteem mediate between perceived early parental love and adult happiness. Applied Psychol 2006;2:38-48. Available at: http://ojs.lib.swin.edu.au/index.php/ejap/article/view/71/100. Accessed June 10, 2010.

3. Monograph on the internet

Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2008. Available at: http://www.nap.edu/books/0309074029/html/. Accessed July 9, 2010.

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Ethyl *p*-methoxycinnamate from *Kaempferia galanga* inhibits angiogenesis through tyrosine kinase

Juni Ekowati*, Suko Hardjono*, and Iwan Sahrial Hamid**

ABSTRACT

BACKGROUND

Many tumors express on their receptor tyrosine kinases vascular endothelial growth factor activity associated with angiogenesis. Inhibition of angiogenesis through reduction of tyrosine kinase activity is a promising strategy for cancer therapy. The present study aimed to determine the mechanism and potency of ethyl *p*-methoxycinnamate (EPMC) isolated from *Kaempferia galanga* as angiogenesis inhibitor.

METHODS

A laboratory experimental study was conducted using chorio-allantoic membranes (CAMs) of nine-day old chicken eggs induced by 60ng basic fibroblast growth factor (bFGF). Ethyl *p*-methoxycinnamate (EPMC) potency was determined at dosages of 30, 60, 90 and 120 μg and compared with celecoxib 60 μg as reference drug and one negative bFGF-induced control group. Neovascularization and endothelial cell count in CAM blood vessels were evaluated. To predict the antiangiogenic mechanism of EPMC, a docking study was performed with the Molegro Virtual Docker program on tyrosine kinase as receptor (PDB 1XKK).

RESULTS

Angiogenesis stimulation by bFGF was prevented significantly ($p<0.05$) by EPMC at dosages of 30, 60, 90 and 120 μg and this activity was dose dependent. Molecular docking showed interaction between EPMC functional groups and tyrosine kinase amino acids at Met766, Met793, Thr854, Thr790, Gln791 and Ala743. There was an association between EPMC antiangiogenic activity and docking study results.

CONCLUSIONS

Ethyl *p*-methoxycinnamate is a potential new angiogenesis inhibitor through interaction with tyrosine kinase. EPMC could be a promising therapeutic agent for treatment of angiogenesis-related diseases.

Keywords: Ethyl *p*-methoxycinnamate, chorio-allantoic membrane, angiogenesis, tyrosine kinase

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Etil p-metoksisinamat dari Kaempferia galanga menghambat angiogenesis melalui interaksi dengan tirosin kinase

ABSTRAK

LATAR BELAKANG

Banyak tumor menunjukkan pada reseptor tirosin kinasenya ekspresi vascular endothelial growth factor yang berhubungan dengan angiogenesis. Hambatan angiogenesis melalui pengurangan aktivitas tirosin kinase adalah strategi yang menjanjikan untuk terapi kanker. Penelitian ini bertujuan untuk menentukan mekanisme dan potensi etil p-metoksisinamat (EPMC) sebagai penghambat angiogenesis.

METODE

Sebuah studi eksperimental laboratorium dilakukan menggunakan chorio-allantoic membrane (CAM) telur ayam tertunas berumur sembilan hari, yang diinduksi dengan basic fibroblast growth factor (bFGF) 60ng. Potensi EPMC diteliti pada dosis 30, 60, 90 dan 120 µg; dibandingkan dengan celecoxib 60 µg sebagai obat referensi dan satu grup tanpa perlakuan. Neovaskularisasi dan sel endotel pembuluh darah baru dari CAM dihitung dan dievaluasi. Untuk prediksi mekanisme antiangiogenesis EPMC, dilakukan studi doking pada reseptor tirosin kinase (PDB 1XKK) menggunakan program Molegro Virtual Docker v.5.5

HASIL

Stimulasi angiogenesis oleh bFGF pada CAM dihambat secara signifikan ($p<0,05$) oleh EPMC pada dosis 30, 60, 90 and 120 µg dan bersifat dose dependent. Celecoxib dan EPMC tersebut menyebabkan terjadinya lisis sel endotel dari CAM. Studi doking menunjukkan adanya interaksi antara gugus fungsi pada EPMC dengan residu asam amino tirosin kinase pada Met766, Met793, Thr854, Thr790, Gln791 dan Ala743. Studi doking dan aktifitas antiangiogenesis EPMC tersebut menunjukkan hasil yang berhubungan.

KESIMPULAN

Etil p-metoksisinamat merupakan senyawa yang berpotensi sebagai angiogenesis inhibitor melalui hambatan pada tirosin kinase.

Kata kunci : *Etil p-metoksinamat, korio allantois membran, angiogenesis, tirosin kinase*

INTRODUCTION

Tyrosine kinase receptors of many tumors express vascular endothelial growth factor (VEGF) activity connected with angiogenesis.[1] In the last decade, angiogenesis has been explored in depth as an interesting cancer therapeutic target, since angiogenesis is an important step in tumor growth and cancer metastasis.[2,3]

Drug resistance, increased tumor progression, and signs of drug toxicity such as bleeding, fatigue, hypertension and gastrointestinal perforation are the main clinical problems that occur in patients treated with angiogenesis inhibitors.[1] Thus, the use of natural herbal alternative agents to constrain angiogenesis is quite crucial in cancer treatment. Ethyl *p*-methoxycinnamate (EPMC), a major constituent of *Kaempferia galanga* Linn. (local name: *kencur*, Fam. *Zingiberaceae*) has been used as sunscreen,[4] analgesic [5] and anti-inflammatory.[6,7] agent, as cyclooxygenase-2 (COX-2) inhibitor, and to treat fibrosarcoma in mice.[8] It is has been established that PGE_2 production in preclinical breast and colon cancer